AF ZRW

PTO/SB/21 (09-04)
Approved for use through 07/31/2006. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Total Number of Pages in This Submission: 25

Application Number	10/735,335
Filing Date	December 12, 2003
First Named Inventor	Doddabele L. Madhavi
Art Unit	1623
Examiner Name	Matthew L. Fedowitz
Attorney Docket Number	BIO 2-016

ENCLOSURES *(Check all that apply)*

- [x] Fee Transmittal Form
  - [x] Fee Attached
- [ ] Amendment/Reply
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [ ] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
- [ ] Certified Copy of Priority Document(s)
- [ ] Reply to Missing Parts/ Incomplete Application
  - [ ] Reply to Missing Parts under 37 CFR 1.52 or 1.53
- [ ] Drawing(s)
- [ ] Licensing-related Papers
- [ ] Petition
- [ ] Petition to Convert to a Provisional Application
- [ ] Power of Attorney, Revocation Change of Correspondence Address
- [ ] Terminal Disclaimer
- [ ] Request for Refund
- [ ] CD, Number of CD(s) _____
  - [ ] Landscape Table on CD
- [ ] After Allowance Communication to TC
- [ ] Appeal Communication to Board of Appeals and Interferences
- [x] Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- [ ] Proprietary Information
- [ ] Status Letter
- [ ] Other Enclosure(s) (please Identify below):

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name	Mueller and Smith, LPA		
Signature			
Printed name	Jerry K. Mueller, Jr.		
Date	October 13, 2005	Reg. No.	27,576

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

Signature	Gail James		
Typed or printed name	Gail James	Date	October 13, 2005

PTO/SB/17 (12-04v2)
Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Effective on 12/08/2004.
Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).

FEE TRANSMITTAL
For FY 2005

☑ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT ($) 250.00

Complete if Known	
Application Number	10/735,335
Filing Date	December 12, 2003
First Named Inventor	Doddabele L. Madhavi
Examiner Name	Matthew L. Fedowitz
Art Unit	1623
Attorney Docket No.	BIO 2-016

METHOD OF PAYMENT (check all that apply)

☑ Check ☐ Credit Card ☐ Money Order ☐ None ☐ Other (please identify): _____

☑ Deposit Account Deposit Account Number: 13-4830 Deposit Account Name: Mueller and Smith, LPA

For the above-identified deposit account, the Director is hereby authorized to: (check all that apply)

☐ Charge fee(s) indicated below ☐ Charge fee(s) indicated below, **except for the filing fee**

☑ Charge any additional fee(s) or underpayments of fee(s) under 37 CFR 1.16 and 1.17 ☑ Credit any overpayments

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

FEE CALCULATION

1. BASIC FILING, SEARCH, AND EXAMINATION FEES

Application Type	FILING FEES Fee ($)	FILING FEES Small Entity Fee ($)	SEARCH FEES Fee ($)	SEARCH FEES Small Entity Fee ($)	EXAMINATION FEES Fee ($)	EXAMINATION FEES Small Entity Fee ($)	Fees Paid ($)
Utility	300	150	500	250	200	100	
Design	200	100	100	50	130	65	
Plant	200	100	300	150	160	80	
Reissue	300	150	500	250	600	300	
Provisional	200	100	0	0	0	0	

2. EXCESS CLAIM FEES

Fee Description	Fee ($)	Small Entity Fee ($)
Each claim over 20 (including Reissues)	50	25
Each independent claim over 3 (including Reissues)	200	100
Multiple dependent claims	360	180

Total Claims _____ - 20 or HP = _____ x Fee ($) _____ = Fee Paid ($) _____

HP = highest number of total claims paid for, if greater than 20.

Indep. Claims _____ - 3 or HP = _____ x Fee ($) _____ = Fee Paid ($) _____

HP = highest number of independent claims paid for, if greater than 3.

Multiple Dependent Claims Fee ($) _____ Fee Paid ($) _____

3. APPLICATION SIZE FEE

If the specification and drawings exceed 100 sheets of paper (excluding electronically filed sequence or computer listings under 37 CFR 1.52(e)), the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).

Total Sheets _____ - 100 = _____ / 50 = _____ (round up to a whole number) x Fee ($) _____ = Fee Paid ($) _____

4. OTHER FEE(S) Fees Paid ($)

Non-English Specification, $130 fee (no small entity discount) _____

Other (e.g., late filing surcharge): Appellants' Brief on Appeal 250.00

SUBMITTED BY

Signature	Jerry K. Mueller, Jr.	Registration No. (Attorney/Agent) 27,576	Telephone 614-436-0600
Name (Print/Type)			Date October 13, 2005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	Doddabele L. Madhavi, *et al.*
Serial No.	:	10/735,335
Filed:	:	December 12, 2003
For:	:	Bioavailable Carotenoid-Cyclodextrin Formulations For Soft-Gels And Other Encapsulation Systems
TC/AU	:	1623
Examiner	:	Matthew L. Fedowitz
Attorney Docket No.	:	BIO 2-016

BOARD OF PATENT APPEALS AND INTERFERENCES
UNITED STATES PATENT AND TRADEMARK OFFICE
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450

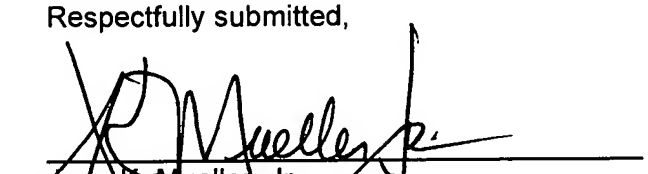
APPELLANTS' BRIEF ON APPEAL

Sir:

Responsive to a Communication mailed July 26, 2005, submitted herewith in triplicate is Appellant's Brief on Appeal as prescribed in 37 C.F.R. § 41.31. Reversal of the primary examiner's rejection of the appealed claims and their allowance is respectfully requested.

The requisite fee of $250.00 as required in 37 C.F.R. § 1.17(c) is submitted herewith. Any additional payments that may be required should be charged to Deposit Account No. 13-4830.

Respectfully submitted,



Jerry K. Mueller Jr.
Reg. No. 27,576
MUELLER AND SMITH, L.P.A.
MUELLER-SMITH BUILDING
7700 Rivers Edge Drive
Columbus, Ohio 43235-1355
tel.: 614-436-0600
fax: 614-436-0057
email: *smueller@muellersmith.com*

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service on October 13, 2005.as first class mail in an envelope addressed to:

Board of Patent Appeals and Interferences
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, Va 22313-1450

Gail E. James

Gail E. James

Real Party in Interest

The appealed application has been assigned by Appellants to and currently is owned by BioActives LLC, a Delaware limited liability company having a business address at 1 Dix Street, Worcester, MA 01609.

Related Appeals and Interferences

There are no related appeals or interferences known to applicant, their legal representatives, or assignee, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

Status of Claims

Twenty claims were submitted with the application as originally filed.

An Office Action was mailed on October 29, 2004, rejecting all of the claims. Appellants filed a response thereto on December 21, 2004. Appellants amended no claims.

An Office Action was mailed on March 14, 2005, rejecting all of the claims. Appellants filed a response thereto on May 2, 2005. Appellants amended no claims.

An Office Action was mailed on July 26, 2005, rejecting all of the claims. Appellants filed a response thereto on August 29, 2005. Appellants amended the claims

An Advisory Action was mailed on September 21, 2005, refusing entry of Appellants' claim amendments. This appeal ensued.

Status of Amendments

The Examiner in an Advisory Action mailed on September 21, 2005 refused to enter the amendments submitted with Appellants' Rule 116 Amendment filed on August 29, 2005.

Summary of the Claimed Subject Matter

The present invention is an improved commercial process for the production of carotenoid-cyclodextrin complexes and formulation of the complex for human ingestion. The carotenoids selected include, *inter alia*, lutein, lycopene, meso-zeaxanthin, and a mixture of lutein:zeaxanthin. The cyclodextrins are selected from among natural cyclodextrins and their derivatives such as, for example, α-, β-, γ-cyclodextrin, and HP-β-cyclodextrin.

The present invention is based on the unexpected discovery that the commercial method of drying and formulation impacts the ability to retain the high bioavailability of lutein from a lutein-cyclodextrin complex. One of the inventive bioavailable forms is a freeze-dried lutein/γ-cyclodextrin complex formulated in lecithin-vegetable oil or vegetable oil for soft gelatin capsules to be used in the nutritional supplement and pharmaceutical industry. The inventive freeze-dried complex shows a highly significant uptake *in vitro* in Caco2 intestinal cells as compared to, for example, a spray-dried complex described in U.S. Patent Application 10/309,999. The complex on formulation shows a significant uptake *in vitro* in the same model based on the excipients used in formulation.

The present invention also is based on the unexpected discovery that the process can be adapted with modifications to other carotenoids, including, *inter alia*, lycopene and mixtures of carotenoids, such as, for example, lutein and zeaxanthin, and to other cyclodextrins such as, for example, α-, β-, γ-, and hydroxypropyl β-cyclodextrins (HP-β).

The present invention further is based on the unexpected discovery that the *in vitro* uptake of lutein and zeaxanthin from the α-cyclodextrin complex is comparable to the γ-cyclodextrin complex neat.

The invention additionally discloses simultaneous uptake of the stereoisomers, lutein and zeaxanthin, from cyclodextrin complexes.

It is totally surprising and unexpected that the method of drying would so dramatically affect the efficiency of recovery of the carotenoid/cyclodextrin complex and the bioavailability of the carotenoid/cyclodextrin complex. These unexpected and surprising results are amply reported in the working examples in the appealed application. For example, Table 1 in Example 1 reports on the effect that drying has on the uptake of lutein from the lutein/γ-cyclodextrin complex by Caco2 cells, *to wit*:

TABLE 1
Effect of Drying on the Uptake of Lutein from the
Lutein/γ-Cyclodextrin Complex by Caco2 Cells

Sample	Cellular Lutein Uptake (Percent Increase)	
	6-hr Incubation	24-hr incubation
Spray-dried Lutein/γ-cyclodextrin Complex	8.75	14.35
Freeze-dried Lutein/γ-cyclodextrin Complex	20.5	56.1

These results show that the cellular uptake was almost 2.5 times as high at 6 hours and almost 4 times as high at 24 hours with the inventive freeze-dried complex compared to the '999 spray-dried complex. The Board will appreciate that we are talking about several orders of magnitude.

The second important comparison in the working examples is reported in Example 5 where a variety of excipients were evaluated, *to wit*, medium chain triglycerides (MCT), polysorbate 80, and a combination of lecithin-soybean oil. The results reported are as follows:

TABLE 5
Effect of Excipients on the Uptake of Lutein from the
Lutein-Cyclodextrin Complex by Caco2 Cells

Formulation	Cellular Lutein Uptake (Percent Increase)	
	6-hr Incubation	24-hr incubation
Free Lutein-Liposome	1.2	1.2
Lutein/cyclodextrin-Polysorbate 80	4.4	10.8
Lutein/cyclodextrin-MCT-	3.2	5.0
Lutein/cyclodextrin-Lecithin-oil	19.0	41.8

These results show that at 6 hours, cellular uptake improved from almost 6 times to almost 16 times; while at 24 hours, cellular uptake improved from almost 4 to 35 times using the vegetable oil excipient. Again, Appellants are showing several orders of magnitude improvement using

freeze-drying and a vegetable oil excipient. While the remaining data will not be repeated here, the honorable Board is urged to review it carefully. Surprising and unexpected results abound in such working examples.

The present invention, then, is a method for making a bioavailable carotenoid-cyclodextrin complex for animal ingestion. This method includes commercial production of the complex and formulating the complex for soft gelatin capsules to retain the properties of the complex. The preferred animal is a human with the route of administration being oral ingestion. The form of the complex for ingestion is a soft gelatin capsule, which may contain other ingredients, both active and inactive. *In vivo*, in a human study, the lutein/γ-cyclodextrin complex improved the absorption of lutein as compared to a commercially available free lutein-oil formulation.

Grounds of Rejection to be Reviewed on Appeal

A. Claims 1-10

Claims 1-10 stand finally rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Leuenberger (U.S. Patent No. 5,221,735), Fukamachi (U.S. Patent No. 4,929,774), Patel (U.S. Patent No. 6,569,463), Orthoefer (U.S. Patent No. 4,125,630), and copending application serial number 10/309,999 (hereinafter, "USSN '999").

Additionally, claim 9 stands rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Patel in view of USSN '999.

B. Claims 11-20

Claims 11-20 stand finally rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Leuenberger, Fukamachi, Patel, Orthoefer, and USSN '999.

Additionally, claims 4,8,14, and 18 stand rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Patel in view of USSN '999.

Additionally, claim 19 stands rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Patel in view of USSN '999.

C. Claims 1-3, 5-7, 9-13, 15-17, and 19-20

Claims 1-3, 5-7, 9-13, 15-17, and 19-20 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of co-pending USSN '999.

D. Claims 1-3, 5-7, 9-13, 15-17, and 19-20

Claims 1-3, 5-7, 9-13, 15-17, and 19-20 stand finally rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over USSN '999.

Argument

The Cited Art

1. Leuenberger

Leuenberger proposes to make a water-soluble inclusion complex of apocarotenal and lycopene with cyclodextrin. The inclusion complex is made generally by dissolving cyclodextrin in water (or other polar solvent) and adding to an organic solvent solution of apocarotenal or lycopene. Organic solvents for the carotenoid include lower alkyl alcohols. (See generally Leuenberger at col. 1, l. 60 bridging col. 2, l. 64). The weight ratio of apocarotenal and lycopene to cyclodextrin "is preferably about 1:10 to about 1:20". (Leuenberger at col. 2, ll. 42-44). Separation of the organic solvent from the inclusion complex includes, "[D]istillation and other methods of solvent removal...known in the art." Leuenberger at (col. 2, ll. 51-42).

At this point in the discussion, the Board's attention is respectfully directed to the Rule 132 Declaration of Dr. Madhavi, which accompanied Appellants' response filed on December 21, 2004. Dr. Madhavi's credentials in the carotenoid field are impeccable. She is a co-inventor of the invention and co-applicant for the above-identified application. With respect to Leuenberger, Dr. Madhavi recites in ¶ 7 that the art has recognized the unpredictability of and difference in properties of inclusion complexes of different cyclodextrin with specific pharmaceuticals and natural compounds. Thus, when forming cyclodextrin complexes in general, the skilled artisan cannot predict with certainty the properties of the resulting complex.

Dr. Madhavi continues that carotenoids and apocarotenoids have varying structures and chemical properties. The number of carbon atoms, ring versus open chain structure, steroisomers, hydrophobicity, *etc.*, are but a few of such recognized general differences. Moreover, because of changes in structure and hydrophobicity, the carotenoids in general show different affinities towards cyclodextrins.

As examples of such complex differences, Dr. Madhavi recites that even within the same class, for example xanthophylls, lutein and zeaxanthin which are stereoisomers, may have different affinities for a cyclodextrin. Lockwood (1996) also has reported that complexation of astaxanthin, another xanthophyll, with sulfobutyl ether beta-cyclodextrin does not improve the solubility to result in a pharmaceutically acceptable chemical delivery system for humans. Also, complexation with cyclodextrins often may not result in increased bioavailbility. For example, according to Spirichev *et al.* (1996) uptake of β-carotene from a cyclodextrin complex was lower as compared to the commercial oil dispersions or microencapsulated beadlets in human studies.

Dr. Madhavi concludes, then, that it is not obvious from the teachings of the art cited against the claims that different carotenoids can be complexed with the natural cyclodextrins or

their derivatives or that complexation in general improves bioavailability. It also is not obvious that a mixture of stereoisomers can be complexed in a manner resulting in simultaneous uptake of the isomers into the cells. Further such teachings do not indicate the variability in uptake based on the cyclodextrins, a factor important for feasibility of commercial production and application of the complex.

It is beyond peradventure that Leuenberger falls woefully short of rendering the appealed claims unpatentable.

2. Fukamachi

Fukamachi proposes to stabilize oxidation-sensitive compounds (vitamins, carotenoids, vitamin A acid, lemon oil—Fukamachi at col. 3, ll. 45-58) against oxidation with a fat (triglyceride—Fukamachi at col. 2, ll. 11-24), a complexing agent (phytic acid, phosphoric acid a polyphosphoric acid, sequestering agents—Fukamachi at col. 2, ll. 25-243), and a coating agent (gelatin, casein, polysaccharide, alginate—Fukamachi at col. 2, ll. 46-55). No cyclodextrins are shown in Fukamachi. To recover a solid product, the dispersion can be subjected to "freeze drying, vacuum drying, spray drying or convection drying" (Fukamachi at col. 3, ll. 26-31). Unfortunately, no freeze-drying is used in any of the working examples—only the other drying methods recited.

In the first instance, Appellants question the use of Fukamachi in forming a rejection, since it is totally devoid of forming any complex in general and no cyclodextrin complexes in particular. With the art recognized lack of predictability of cyclodextrin/carotenoid complexes, what motivation was there for the Examiner to select Fukamachi? Appellants see none, but for the impermissible use of hindsight. Fukamachi adds nothing of vitality to an already weak Leuenberger citation. Moreover, Fukamachi does not reduce freeze-drying to practice, so that the Fukamachi does not teach nor can the skilled artisan learn from Fukamachi that freeze-drying of a cyclodextrin/carotenoid complex would have improved bioavailability, which has been demonstrated in the working examples in the appealed application.

3. Orthoefer

Orthoefer proposes vegetable proteins for use as extenders or textured vegetable proteins in meat analogs. The Examiner cites Orthoefer as teaching edible triglyceride oils. For such proposition, Appellants have no disagreement. As for Orthoefer itself, it shows no carotenoids, no cyclodextrins, no carotenoid/cyclodextrin complexes, no improved bioavailability of any substance, *etc.* Again, selection of Orthoefer to be held against the claims seems again to have come from impermissible hindsight. That is, the Examiner looks at the invention and

then finds any catch-as-catch can reference that includes any ingredient recited in the claims. The after-the-fact justification that Orthoefer teaches edible substances begs the question, since Appellants are not claiming foodstuffs in general, but rather are claiming cyclodextrin/carotenoid complexes.

4. Patel

Patel proposes to provide solid pharmaceutical compositions of a solid carrier and encapsulation coating. The coating can include pharmaceutical active agents, hydrophilic surfactants, hydrophobic surfactants, and triglycerides. Alternatively, the solid carrier can include the pharmaceutical active agents, hydrophilic surfactants, hydrophobic surfactants, and triglycerides. Processing includes any known technique (see Patel at col. 4, ll. 9-19).

Pharmaceutical active ingredients include, *inter alia*, carotenes, lutein, lycopene from a list that spans some 5 columns. Several columns of surfactants and coating agents also are shown. Among the "solubilizers" are cyclodextrins from a list that spans over a column of listed solubilizer agents.

No cyclodextrin complexes appear to be shown in general much less carotenoid/cyclodextrin complexes in particular. Again, considering the art recognized lack of predictability in the properties of such complexes, Patel is seen as adding nothing. Again, the Examiner seems to have selected references based on laundry lists of ingredients, rather than based on teachings vis-à-vis the invention. Patel itself does not single out complexes of cyclodextrins with carotenoids. The case law is consonant that teaching does not arise out of after-the-fact selection of ingredients from long laundry lists of ingredients where the reference provides no teaching of such combination.

5. USSN '999

<u>The Appealed Invention is Patentable Over USSN '999</u>

USSN '999 teaches the skilled artisan the following, vis-à-vis, drying:

> The coated products may be dried, if desired, by customary methods, but not limited to freeze drying and spray drying, <u>preferably spray drying</u>.
>
> USSN '999 at ¶ 0019 (emphasis supplied).

> Spray drying is an especially useful method of preparing the coated complex formulations. Conventional spray dryers may be used, with single or multiple nozzles, disk atomizers, tangential spray, etc. Hot air flow may be concurrent or

> countercurrent, sand spray may be top spray, wurster or bottom spray, tangential spray ,etc.
>
> USSN '999 at ¶ 0022.

The working examples in USSN '999 show only <u>one</u> drying technique—spray drying. See Example 1 ("spray dried at 180° C."), Example 2 ("spray dried at 180° C."), Example 3 ("spray dried at 180° C."), Example 7 ("spray dried in a conventional spray drying apparatus having two spray nozzles"), Example 8 ("sprayed at 5 ml/min from the bottom of the drying chamber"), Example 9 ("sprayed at 10 ml/min from the bottom of the drying chamber").

Dr. Madhavi's and Dr. Kagan's declaration confirm this drying teaching in USSN '999 by stating, *inter alia*, "spray drying was the only drying method studied and actually reduced to practice" (¶ 13 of the Madhavi/Kagan declaration). They further state, *inter alia*, "they had no idea that the method of drying would affect the recovery and bioavailability of the carotenoid/cyclodextrin complexes" (¶ 14 of the Madhavi/Kagan declaration). These statements come from the inventors of the USSN '999 invention and from an admitted expert in the field, Dr. Madhavi. Such statements do not compromise the vitality of the USSN '999 invention; but, they do resound in an understanding or assumption that the USSN '999 inventors had with respect to the method of drying the carotenoid/cyclodextrin product. This fact is accentuated in the laundry list of drying methods set forth in USSN '999. No difference in drying was known to the USSN '999 inventors and only spray drying was reduced to practice.

Despite such teachings in the art, Dr. Madhavi and Dr. Kagan began to test methods of drying of the complex and were astounded to determine that the method of drying dramatically affected the efficiency of recovery of the complex and the bioavailability of the complex. There is no way that the USSN '999 inventors could have known and/or predicted these results without having actually tested different drying methods. Since the USSN '999 inventors did not actually try (reduce to practice) and compare different drying methods, USSN '999 does not render obvious the surprising and unexpected results now reported in the above-identified application.

The Board is reminded of the data in the appealed application and summarized above on the effect of drying on the uptake of lutein from the lutein/γ-cyclodextrin complex by Caco2 cells, as reported in Example 1. These results show that the cellular uptake was **almost 2.5 times as high at 6 hours and almost 4 times as high at 24 hours** with the inventive freeze-dried complex compared to the '999 spray-dried complex. The Board will appreciate that we are talking about several orders of magnitude.

The Board is further reminded of the data in the appealed application and summarized above on the effect of excipients on the uptake of lutein from the lutein-cyclodextrin complex by

Caco2 cells. These results show that at 6 hours, cellular uptake improved from almost **6 times to almost 16 times; while at 24 hours, cellular uptake improved from almost 4 to 35 times** using the vegetable oil excipient. Again, Appellants report several orders of magnitude improvement of the invention compared to USSN '999.

It is beyond peradventure to postulate that USSN '999 teaches the skilled artisan any other drying technique than spray drying. Even though a laundry list of drying methods is recited, the only detailed description of equipment and conditions is for spray drying and the only reduction to practice reported is for spray drying. Between the several conventional techniques recited in USSN '999, the skilled artisan would expect equivalent, if not superior, results using spray drying compared to any other technique. The same conclusion can be drawn for the excipient of choice, *i.e.*, equivalent results should be expected using any of the named classes of excipients.

To the contrary, however, Appellants discovered quite unexpectedly that bioavailability would be dramatically improved (many orders of magnitude) if the processor uses freeze-drying and vegetable oil excipients. These are exactly the unexpected and surprising results required by the courts to rebut a *prima facie* case of obviousness. "That is may have been obvious to try, however, is not a legitimate test of patentability under 35 U.S.C. § 103." *In re Fine*, 5 USPQ2d 1159, 1599 (Fed. Cir. 1988). "The most that may gleaned from the Tiao et al. reference, therefore, is an assumption that it would have been obvious to try, albeit without any expectation of success, the claimed activatable complexed metal catalyst in combination with the claimed heat-activatable amine or amine-like catalyst. That it would have been obvious to try is not, however, the standard of invention." *In re Tomlinson*, 150 USPQ 623, 626 (CCPA 1966).

Similarly, the rejection of the appealed claims is not more than an "obvious to try" rejection. The law requires more. Based on the clear teachings in USSN '999, the skilled artisan would be biased to drying by spray drying. There is no expectation that if the skilled artisan employed a non-preferred drying technique (*i.e.*, freeze-drying) that many-fold orders of magnitude of bioavailability would be achieved. In many respects, USSN '999 teaches away from the appealed invention by teaching the skilled artisan that the products "may be dried, if desired, by...preferably spray drying." In fact, USSN '999 qualifies product recovery by stating that that the skilled artisan, "if desired" may dry the product. This statement teaches that drying is not even necessary, but if it is used, the skilled artisan should use spray drying.

In summary, Appellants have rebutted the *prima facie* case of obviousness given by the Examiner by establishing (1) "the existence of unexpected properties in the range claimed" or (2) "that the art in any material respect taught away" from the claimed invention." *In re Geisler*,

43 USPQ2d, 1362 (Fed. Cir. 1997), applying the "*Malagari*" test in *In re Malagari*, 182 USPQ 553, 549 (CCPA 1974).

USSN '999 is Not an Invention by "Another"

In order for a patent to be prior art under §102(e), and hence available under 103(a), it must be "by another." Under this rule "only one inventor need be different for the inventive entities to be different...." MPEP § 706.02(f). Thus, the inventive entity A, B, and C is different from the inventive entity of A and B. It should be noted, however, that to resolve the issue of whether or not there is a different inventive entity, one must "look beyond the superficial fact that the references were issued to different inventive entities. What is significant is not merely the differences in the listed inventors, but whether the portions of the reference relied on as prior art, and the subject mater of the claims in question, represent the work of a common inventive entity." *Riverwood Int'l Corp. v. R.A. Jones & Co., Inc.*, 66 U.S.P.Q.2d 1331, 1338 (Fed. Cir. 2003).

In this case, USSN '999 lists Dr. Madhavi, Dr. Kagan and Helmet Reuscher, while the present application lists Drs. Madhavi and Kagan alone. As the law prescribes, however, this does not end the analysis. The declaration of Drs. Madhavi and Kagan affirmatively states that the third inventor's contribution to the USSN '999 application was for certain polymer coatings that were applied to the carotenoid/cyclodextrin complexes. Madhavi/Kagan Declaration at ¶ 11. The carotenoid/cyclodextrin complexes themselves were the joint invention of Drs. Madhavi and Kagan. Madhavi/Kagan Declaration at ¶¶ 9-10, 12. Thus, any and all disclosure from the USSN '999 application cited by the Examiner as prior art was invented by Appellants, Drs. Madhavi and Kagan. Because Drs. Madhavi and Kagan are jointly the inventors of the claimed invention in the present application, the cited subject matter is not "by another" and cannot be prior art to the claims at issue.

6. Combination of Leuenberger, Fukamachi, Patel, and Orthoefer

With respect to the inclusion of a vegetable oil and the freeze-drying of the complex, Leuenberger describes use of oil to dissolve/disperse carotenoids followed by emulsification with water. Fukamachi describes use of vegetable oils in microencapsulation formulations for oxidation sensitive compounds and mentions lutein and zeaxanthin. However, the oils are used for making an emulsion with the gelatin matrix, an application entirely different from using the oil as an excipient or filler for the cyclodextrin complex, as in the present invention. Orthoefer teaches using triglycerides as plasticizers for making meat analogs from vegetable proteins, again an application entirely different from formulating a carotenoid-cyclodextrin complex into a

dosage form as in the present invention. Patel teaches the use of surfactants in the formulation. Again, it is not obvious from these teachings whether a carotenoid cyclodextrin complex can be formulated with these excipients without any adverse effects on the stability of the complex or the bioavailability.

Dr. Madhavi's declaration speaks to this issue also. She notes that the weak cyclodextrin/carotenoid bonds can be disrupted by a number of factors, including, *inter alia*, excipients used in formulations, including, *inter alia*, vegetable oils, medium chain triglycerides, and synthetic surfactants such as polysorbates, polyethylene glycols, and phospholipids such as lecithin. She continues that excipients with different polarities may interact with cyclodextrins resulting in the dissociation of the complex, inhibit the release of the actives, or modulate the dissolution properties. The interactions in general are often unpredictable in her expert opinion. Dr. Madhavi cites several publications on the interactions of cyclodextrin inclusion complexes of pharmaceuticals and flavor compounds with formulation excipients.

Again, the art combination structured in the claims rejections do not provide the certainty in teaching regarding the vegetable oil portion of the inventive product and process insofar as expected stability of the complex is concerned. The art, then, falls far short of rendering unpatentable the present invention.

With respect to the drying method used in forming the complex, Dr. Madhavi emphasizes the data reported in the working examples in the above-identified application. She states that the invention describes a commercially efficient process, which includes freeze-drying an aqueous dispersion of carotenoid-cyclodextrin complex. Freeze-drying was found to be efficient as compared to spray-drying with a 95% recovery of the product, as compared to 50% loss with spray-drying. Further, to her surprise, the freeze-dried product was superior to spray dried product in bioavailability studies. This unexpectedness is not dispelled or compromised just because freeze-drying is known in the art. The unexpectedness is that for Appellants' product only freeze-drying provided improved bioavailability for the product. Such unexpectedness testifies to the surprising and unexpected results achieved by the invention, which cannot be predicted.

Dealing with the soft gel issue, Dr. Madhavi notes that it is well known in the art that hydrophobic compounds present delivery challenges because of their physicochemical properties and soft gelatin capsules may offer a delivery system. However, complexation of carotenoids with cyclodextrins in general resulted in a hydrophilic, water dispersible fine powder. Such complexes are used for making directly compressible tablets or incorporated in to hard gelatin capsules, as cyclodextrins are expected to stabilize sensitive compounds against degradation. However, Dr. Madhavi and her co-inventor found that complexation with

cyclodextrins did not stabilize the carotenoids to afford the necessary commercially accepted shelf life in tablets or hard capsules. The soft-gelatin formulation was developed to stabilize the carotenoids. Again, this cannot be predicted and is unexpected.

Dr. Madhavi further states that when hydrophobic excipients, such as vegetable oils, are used, they may inhibit the dispersion of the complex in water; thus, reducing the uptake of the active molecule. However, to her surprise, she found that the complex retained its properties even after formulation with vegetable oil or vegetable oil-lecithin as excipients.

Dr. Madhavi concludes that in her opinion, it was totally unexpected that a commercially feasible, practical, and commercially viable process resulted for making a bioavailable cyclodextrin/carotenoid complex by freeze-drying a cyclodextrin/carotenoid complex in a molar ratio of between about 0.5:1 and 10:1, and adding such freeze-dried complex to a vegetable oil. The art cited simply does not render obvious the present invention in her expert opinion.

Conclusion

Accordingly, Appellants respectfully urge the Board to overrule the rejection of the appealed claims and to permit the appealed application to pass to issue.

Respectfully submitted,

Jerry K. Mueller, Jr.
Reg. No. 27,576
MUELLER AND SMITH, L.P.A.
Mueller-Smith Building
7700 Rivers Edge Drive
Columbus, Ohio 43235-1355
tel.: 614-436-0600
fax: 614-436-0057
email: *smueller@muellersmith.com*

CLAIMS APPENDIX

The Appealed Claims

Claim 1. A bioavailable cyclodextrin/carotenoid complex, which comprises:

(a) a freeze-dried cyclodextrin/carotenoid complex in a molar ratio of between about 0.5:1 and 10:1; and

(b) a vegetable oil.

Claim 2. The complex of claim 1, wherein said vegetable oil is edible.

Claim 3. The complex of claim 2, wherein said vegetable oil is one or more of cocoanut oil, corn oil, cottonseed oil, oat oil, olive oil, palm oil, palm kernel oil, peanut oil, rapeseed oil, rice bran oil, safflower oil, sesame seed oil, soybean oil, or sunflower oil.

Claim 4. The complex of claim 1, wherein lecithin is admixed with said vegetable oil in a weight ratio of lecithin to vegetable oil ranging between about 10:1 and 1:1.

Claim 5. The complex of claim 1, wherein said cyclodextrin is one or more of α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, or HP-β-cyclodextrin.

Claim 6. The complex of claim 1, wherein said carotenoid is one or more of lycopene, lutein, or zeaxanthin.

Claim 7. The complex of claim 5, wherein said carotenoid is one or more of lycopene, lutein, or zeaxanthin.

Claim 8. The complex of claim 7, wherein lecithin is admixed with said vegetable oil in a weight ratio of lecithin to vegetable oil ranging between about 10:1 and 1:1.

Claim 9. The complex of claim 1 disposed in soft gelatin capsule.

Claim 10. The complex of claim 8 disposed in a soft gelatin capsule.

Claim 11. A method for making an improved bioavailable form of cyclodextrin/carotenoid complex, for animal ingestion, which comprises the steps of:

(a) forming a cyclodextrin/carotenoid complex;

(b) freezing drying said cyclodextrin/carotenoid complex;

(c) blending said freeze-dried cyclodextrin/carotenoid complex with a vegetable oil; and

(d) incorporating said blend into a soft gelatin capsule.

Claim 12. The method of claim 11, wherein said vegetable oil is edible.

Claim 13. The method of claim 12, wherein said vegetable oil is one or more of cocoanut oil, corn oil, cottonseed oil, oat oil, olive oil, palm oil, palm kernel oil, peanut oil, rapeseed oil, rice bran oil, safflower oil, sesame seed oil, soybean oil, or sunflower oil.

Claim 14. The method of claim 11, wherein lecithin is admixed with said vegetable oil in a weight ratio of lecithin to vegetable oil ranging between about 10:1 and 1:1.

Claim 15. The method of claim 11, wherein said cyclodextrin is one or more of α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin, or HP-β-cyclodextrin.

Claim 16. The method of claim 11, wherein said carotenoid is one or more of lycopene, lutein, or zeaxanthin.

Claim 17. The method of claim 15, wherein said carotenoid is one or more of lycopene, lutein, or zeaxanthin.

Claim 18. The method of claim 17, wherein lecithin is admixed with said vegetable oil in a weight ratio of lecithin to vegetable oil ranging between about 10:1 and 1:1.

Claim 19. The method of claim 11, wherein said cyclodextrin/carotenoid complex is made for human ingestion.

Claim 20. The method of claim 18, wherein said cyclodextrin/carotenoid complex is made for human ingestion.

EVIDENCE APPENDIX

1. Declaration under 37 C.F.R. § 1.132 of Doddabele L. Madhavi, Ph.D., submitted with Appellants' response of December 21, 2004.

2. Declaration under 37 C.F.R. § 1.132 of Doddabele L. Madhavi, Ph.D. and Daniel I. Kagan, Ph.D. submitted with Appellants' response of May 2, 2005.

RELATED PROCEEDINGS APPENDIX

None.